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<b>(54) Title:</b> SYSTEMIC DRUG DELIVERY SYSTEM THROUGH APPLICATION ON NAILS  <b>(57) Abstract</b>  A method is provided for administering a therapeutically active substance to a subject, which comprises applying the substance to the surface of one or more fingernails and/or toenails whereby the substance is absorbed and transported systemically to a site of action remote from the finger or toenail.		

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## SYSTEMIC DRUG DELIVERY SYSTEM THROUGH APPLICATION ON NAILS

This invention relates to a novel delivery system for achieving systemic delivery of drugs and other agents with pharmacological or physiological action and more specifically to a novel method of administering a therapeutically active substance to a subject. The term "therapeutically active substance" is intended also to include substances having a physiological, pharmacological or prophylactic effect.

In many areas of pharmacology it is desirable to devise new routes of administration for therapeutically active substances. Thus, for example, in many instances normal routes of administration such as administration by mouth or parenteral administration are inconvenient or inappropriate, such as, for example, where a prolonged sustained release effect is required or if a therapeutically active substance is likely to be degraded rapidly if administered via customary routes. Also, in cases where a therapeutically active substance needs to be administered continuously at a low, but sustained dosage rate (for example to provide a constant plasma concentration without peaks and troughs), available dosage forms often fail to achieve the desired effect, or the therapeutically active substance needs to be administered in a form which is inconvenient or dangerous to use, or which is expensive to manufacture.

Thus, for example, although single shot depot contraceptives and steroids often function satisfactorily, once a depot contraceptive or steroid is administered, its action cannot be quickly and readily reversed. Similarly, it is often difficult to prepare a sustained release dosage form for oral administration which can reliably release a controlled amount of therapeutically active substance over a long period of time. Furthermore, a given sustained release capsule or pill will release its active ingredient at a particular rate. Accordingly in order to provide the possibility of varying the dosage rate, either a pharmaceutical supplier has to provide a number of different dosage forms, each with a different release rate, or a physician will

need to attempt to control the release rate by prescribing different numbers of dosage units. Each of these proposals has attendant disadvantages.

It is thus generally accepted that improvements are needed in the modes and methods of administration of therapeutically active substances. This applies both for the effect of drugs acting locally as well as the effect of drugs which are absorbed into the blood, lymphatic and tissue fluids, and transferred systemically for an action at sites distant from the point of application, for which latter purposes drugs are traditionally given orally or parenterally. The present invention is specifically concerned with the drugs and biologically active agents administered for systemic action at sites distant from the point of application.

Improvements in this field may, for example, be necessary simply to provide alternatives available for patient preference or convenience, or to allow greater compliance: thus there may be objections to oral, rectal, sublingual or intravenous routes of administration. In some instances there may be a need to overcome first pass metabolic degradation of drug in the liver, or variation in drug handling, consequent on concentration, or dose-related kinetics. Again, to achieve an optimal effect, there may be a need to keep the dosage constant, as well as a necessity to avoid the peaks of blood concentration of drug, such as occur when drugs are given orally or parenterally in a dose necessary to achieve a particular effect: abolition of peaks and maintaining a constant plasma concentration would reduce some wanted effects and increase patient compliance. Maintaining a constant effect by stable blood concentration, is difficult to sustain by oral or parenteral administration because peak concentrations are followed by a decline; with depo-injection a more constant level may be achieved, but it is difficult to remove the drug, for example if unwanted effects are encountered in the course of such administration.

To overcome some of these problems, sustained dosage release patches have been introduced, first for scopolamine (hyoscine) and now for other substances e.g. nitroglycerin, oestradiol, clonidine, fentanyl and nicotine, (see e.g.

## 3

EP-A-O 117 027). Whilst these have many of the advantages mentioned above, their use has been limited to these and a few other drugs because the use of patches does not overcome the problem of the impermeability of the stratum corneum of the skin, and the need to use a patch of acceptable size. Thus a relatively small daily dose of drug can be administered - usually the order of 0.2-20 mg per day. Furthermore, because of the permeability characteristics of the stratum corneum of the skin, the nature of the drug which can be delivered by patch is seriously restricted both by the size of molecule, which generally needs to be less than 1000 daltons, and by the need for a critical lipid/water solubility. Attempts to enhance the absorption through the skin have been made using hydrating agents such as urea, various penetration enhancing agents such as dimethylsulphoxide and similar compounds, pyrrolidones, fatty acids, Azone, surfactants, alcohols, glycols, essential oils, terpenes, terpenoids and their derivatives and amines (see, e.g. "Skin Absorption Enhancers", Williams, A.C. et al., Critical Reviews in Therapeutic Drug Carrier Systems, 9(3,4): 305-352 (1992)) and a range of proteolytic enzymes such as papain, but although these do enhance penetration, they have not allowed the marketing of new systems for delivery of drugs other than oestradiol through the stratum corneum of the skin. In addition there is a risk of irritation and contact sensitization initiated through skin Langerhans cells resulting in a comparatively high incidence of unwanted local effects, particularly with drugs such as nicotine. (Examples of percutaneous formulations for administering nicotine as part of a regime for aiding smokers to reduce their dependence upon tobacco are given in EP-A-O 289 342 and CA-A-1 273 878). Also many object to the use of an obvious patch on the skin. Thus it appears that further improvements to the existing systems are desirable.

The use of iontophoresis and electroporation has been proposed for augmenting drug delivery through the skin but there are many problems associated with safety, convenience and expense. For example, GB-A-2 206 493 describes an iontophoresis device for percutaneous or perungual administration of a dissolved substance, for example a drug. In use, a pair of electrodes are attached to a patient's skin or nail, separated by a pad of electrolyte and an e.m.f. of typically

1.35 - 1.83 volts applied. There is no suggestion of administration of any substance percutaneously or perungually in the absence of an applied e.m.f., i.e. by passive absorption, as in the present invention.

Attempts have been made to enhance penetration of therapeutically active substances through the stratum corneum by using penetration enhancers such as dimethylsulphoxide, see e.g. GB-A-2 057 263, but the use of such penetration enhancers are generally restricted to compositions in liquid form and provide problems with respect to registration with drug registration bodies. Further, dimethylsulphoxide is irritant and toxic.

By contrast, the application of therapeutically active substances to finger and toe nails has been reported for the specific purpose of applying antifungal agents or antibiotics adapted to treat infections of the nail. Thus, for example, EP-A-O 515 312 discloses topical formulations containing terbinafine in the form of nail varnishes designed to treat onychomycosis. WO-A-87/02580 describes further examples of compositions for delivering drugs topically to human nails. However all such compositions are restricted to uses wherein the composition is intended for local action without transport of the therapeutically active substance to the site remote from the finger or toe nail, in particular to a systemic tissue compartment. Thus an article entitled "Topical and Systemic Absorption of Sodium Pyrithione following Topical Application to the Nails of the Rhesus Monkey", Mayer, P.R. et al., Skin Pharmacol. 1992; 5:154-159 describes the fate of radio-labelled pyrithione applied to finger nails and toenails of rhesus monkeys and states that "only slight drug concentrations were measurable in plasma". Further in a description of a parallel human study, it was stated that "less than 10% of patients... had quantifiable concentrations (greater than 10 ng/ml ) of 2-methylsulfonyl pyridine... a long-lived metabolite which is a marker of systemic exposure to pyrithione derivatives".

A further article entitled "Permeability characteristics of the human nail plate", Walters K.A. et al., International Journal of Cosmetic Science 5, 231-246

(1983) discusses the differences between the permeabilities of skin and nails to various substances, especially ingredients of cosmetics. The article concludes that "it may soon be possible for the pharmaceutical manufacturer to chemically tailor drugs which will prove more effective in the topical management of nail infections. Further it also appears that cosmetic scientists will soon be able to more prudently select the raw materials for nail products to minimize the troubling consequences of perungual absorption". (See also "Physicochemical characterization of the human nail: permeation pattern for water and the homologous alcohols and differences with respect to the stratum corneum", Walters, K.A. et al, J. Pharm. Pharmacol. 1983, 35: 28-33 and "Penetration of chemicals into, and through, the nail plate", Walters, K.A., Pharmacy International, April 1985, pp 86-89). Such publications teach away from the use of nails for systemic administration of drugs.

The present invention which has all the advantages of the patch system, but without the disadvantages, is based upon a surprising discovery that finger nails and toe nails provide an effective route of systemic administration for a wide range of therapeutically active substances by simple local application. Nails also have the advantage that drug delivery through them is not complicated by the presence of hair follicles and sweat glands, as in skin, nor the very wide variation in permeability of the stratum corneum at different body sites and in different individuals.

Thus according to the present invention there is provided a method of administering a therapeutically active substance to a subject, which comprises applying the substance to the surface of one or more finger or toe nails whereby the substance is absorbed and transported systemically to a site of action remote from the finger or toe nail.

The invention further provides the use of a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical composition adapted for application to finger nails and/or toe nails, characterised in that the composition contains at least one therapeutically active substance whereby in use the substance is

absorbed and transported systemically to a site of action remote from the finger or toe nail.

The use of a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical composition adapted for application to finger nails and/or toe nails, characterised in that the composition contains at least one therapeutically active substance which is capable of passing from the applied composition, through the nail to which it is applied, and into a systemic tissue compartment also forms an aspect of the invention.

In carrying out the invention the therapeutically active substance may be applied in the form of a composition comprising one or more components for promoting retention of the composition within or on the nail surface. Thus, for example, the composition may comprise a film-forming component or it may be in the form of a varnish, lacquer, gel or solution. Alternatively the substance may be applied to the nail in a patch. Film-forming components may be chosen so as to modulate the rate of penetration of the therapeutically active substance. I.e. it may enhance or restrict the rate of penetration or it may allow the nail itself to act as a reservoir. Alternatively or additionally, the composition may include an additional component which has the capacity to modulate the rate of penetration of the therapeutically active substance in this way. Again the composition may itself enter the nail and modulate the inward absorption of the drug. Agents may also be added to decrease local effects such as irritancy arising from the therapeutically active agent or components of the formulation.

It is to be understood that the method of the invention does not require the application of electrodes to the finger or toe nails in order to provide an e.m.f. which promotes transport by electrophoresis or iontophoresis. On the contrary the therapeutically active substance is transported passively through the finger or the toe nail in accordance with the invention. The term "passively" (and derived terms) as used herein is intended merely to refer to the absence of an applied e.m.f. to electrodes. Passive transport in accordance with the invention can



include transport by diffusion as well as transport that is mediated by physiological processes or by the application of penetration enhancers.

All formulation types which have generally been applied to the skin and hair may, with suitable adaptation, be applied to nails.

As indicated, the method of the invention is applicable to administration of a wide variety of therapeutically active substances including, for example, ones having a therapeutic effect on the central nervous system, cardiovascular system, endocrine system or respiratory system as well as therapeutically active substances having an analgesic or anti-allergic effect. Similarly, the method of the invention may be applied to the administration of therapeutically active substances which have a therapeutic effect on the gastrointestinal tract or the genito-urinary system or ones which have a contraceptive activity. The therapeutically active substances can include not only chemically synthesized drugs, but also biologically-derived molecules, for example physiological substances such as growth factors, hormones and their release factors, enzymes and lymphokines. The substances to be delivered may act as vaccines or immunomodulators.

Other examples include anti-infective agents, for example antibiotics (including antimicrobial and antiviral drugs), drugs which affect metabolic processes such as calcium transport, iron metabolism and metabolic processes involving folic acid, cytostatic and anti-neoplastic drugs, haematopoietic drugs and drugs that act on the muscular/skeletal, neural and neuromuscular system. Other therapeutically active substances include ones which affect gene structure and function. The therapeutically active substance can have dermatological activity although it is to be understood that such activity should be at a site distal from the site of application to the nails. Drugs that act on oral tissues, e.g. drugs for treating dental or gingival pathologies are also included.

The substances to be delivered by the method of the invention may have an effect on pathological disorders which involve single or many body systems

including those whose mechanism is still uncertain. It may also be used prophylactically or for physiological or social purposes. The method can be used for the delivery of substances acting on any bodily system, organ or tissue in health or disease.

It is to be understood that the term "therapeutically active substance" as used herein is intended to extend not only to substances which have a therapeutic action *per se*, but also to substances which comprise so called "pro-drugs", i.e. substances which convert to a therapeutically active form on administration. Similarly, the term "therapeutically active substance" extends not only to substances which are specifically adapted to cure or ameliorate the symptoms of a disease, but also to substances which have a palliative effect as well as substances which are used as so-called "recreational" drugs. One example in this connection is the use of the method of the invention for administering nicotine as part of a therapy designed to wean a tobacco smoker from his or her addiction.

The invention will now be described in more detail with particular reference to the accompanying drawings of which

Figure 1 depicts the results of an experiment measuring trans ungual water loss.

Figure 2 depicts the results of an experiment measuring water loss with increasing stripping (as a normal curve).

Figure 3 depicts the results of an experiment measuring cumulative penetration of (<sup>3</sup>H)-Nicotine through human nail following a single application of a 50% (v/v) solution in 0.1 M HEPES buffer, pH 7.4.

Figure 4 depicts the results of an experiment measuring cumulative penetration of (<sup>3</sup>H)-Clonidine through human nail following a single application of a 52.8 mg/mL solution in 0.1 M HEPES buffer, pH 7.4.

Figure 5 depicts the results of an experiment measuring cumulative penetration of (<sup>3</sup>H)-DAGO through human nail following a single application of an 8 mg/mL solution in 0.1 M HEPES buffer, pH 7.4.

Figure 6 depicts the results of an experiment measuring cumulative penetration of (<sup>3</sup>H)-Propranolol through human nail following a single application of a saturated solution in 0.1 M HEPES buffer, pH 7.4.

Figure 7 depicts the results of an experiment measuring cumulative penetration of (<sup>3</sup>H)-Melatonin through human nail following a single application of a saturated solution in 0.1 M HEPES buffer, pH 7.4.

The precise mechanism by which therapeutically active substances are transported to their site of action in accordance with the invention has not been fully determined, nor is it known what factors limit the passage of therapeutically active substances through the nail. However it is believed that the major factor which contributes to the efficacy of the invention is the high water permeability of the nail plate. Thus experiments have shown that the rate of water transport through the nail plate can be up to 10 times the corresponding rate through the stratum corneum of the normal epidermis (see Waters K.A. et al., J. Pharm. Pharmacol. 1983, 35, 28-33 and Figs. 1 and 2). An early paper (Johnson and Shuster 1974) discussed the permeability of the stratum corneum to water and more recently experiments have been described which have used water flux to demonstrate and quantify the permeability characteristics of the stratum corneum (Puttick & Shuster 1985, Brit. J. Dermatol., 113, 775). Similar methods were then applied to the nail *in vivo* and *in vitro* (Johnson & Shuster - unpublished). Thus it was found that the rate of water transmission through nail and stratum corneum is dependent on their thickness. This is illustrated graphically in Figs. 1 and 2

respectively. When these earlier findings on the water permeability of the stratum corneum of the skin were compared with those of the nail it was observed that surprisingly the nail was 5 to 10 times more permeable to water than skin, despite the 100-fold greater thickness of the nail plate than the stratum corneum. Thus when expressed per unit of thickness, the nail is 1000 times more permeable than skin. More importantly in the present context it was realised that this greater permeability could be applied to the inward carriage of substances such as drugs and prodrugs. Furthermore, by using all 20 nails it was realised that the nail could be made to absorb drug at a rate of 100 times more rapidly than the skin, and even more rapidly if the nails were treated as discussed below. Furthermore, from knowledge of the nature of the nail it was concluded that lipid solubility would be less critical than in the stratum corneum of skin, and more importantly, the limiting molecular size of certain drugs capable of being absorbed systemically after application to the nail would be appreciably greater than for stratum corneum. Finally because of the 100 fold greater thickness of nails, it was realised that the nails could serve as a large and effective reservoir of drugs, an effect most notably established in the stratum corneum for topical corticosteroids. From these findings it is apparent that because of the much greater thickness of nails and the much larger total surface area of all the nails than that which can be provided for certain drugs by a conventional patch delivery system, the reservoir or storage effect would be several hundred fold greater in the nail than in the stratum corneum under a conventional patch delivery system. Also a larger reservoir would be provided than in a conventional patch delivery system.

It has thus now become apparent that the nail can be used for the controlled delivery of a very large range of drugs. The carrier to be used can vary with the different drugs; thus it could be, for example, in the form of a conventional nail lacquer, a peel-off applicator, a water soluble drying gel, a stable emulsion, an aerosol or liposomal or lipid or cream base; likewise a simple alcoholic or aqueous solution could be used, the choice depending on the characteristics of the drug to be delivered and the dosage required. Likewise the drug application could be made in one particular carrier in which the drug or prodrug could be dissolved or

suspended, and then the whole covered by further material, e.g. a conventional lacquer, a water-soluble peel-off base or in some circumstances an occlusive dressing or patch containing an additional reservoir of drug, with or without its own membrane. Thus, an advantage of the invention is that a large range of carrier bases can be used and selected so that the effect of the nail itself could be optimised to act both as a reservoir and rate limiting delivery system for the applied drug, by using partitioning between the vehicle and nail and subsequent systemic absorption from the nail. In addition to this method of controlling systemic absorption from the nail, the absorptive characteristics of the nail could themselves be modified: thus nail thickness could be decreased e.g. by abrasion and other physical methods, and modifiers of permeability could be used e.g. using penetration enhancers as previously mentioned or enzymes to enhance delivery. In other instances systemic absorption of drug from the nail could be limited by maintaining nail dehydration e.g. by using a hypertonic solution. The use of the nail as a reservoir for the absorbed drug can be modulated in several ways. By prior application of saturated or even supersaturated solutions of drug the nail reservoir can be rapidly filled after which continued constant absorption can be achieved by further surface application as described. In addition, by application of a suitable source of fluid to the nail surface (e.g. in a pad), drug can be rapidly extracted from the nail and its effect thereby terminated. Variations in such application would also permit specifically designed pulsed absorption of drugs.

Furthermore, since the rate of delivery is related to the surface area of the nail, and since each nail has a different surface area and thickness, enabling a consistently different water flux (varying from for example 9 to 13 g/m<sup>2</sup>/hr in one study going from the first to the fifth digit on the hand and similarly for the feet), it will be possible to use nails singly or in combination to control the dose of drug absorbed by a range of some 50-fold. Thus the method provides a unique control of dosage delivery.

As indicated, in making the present invention available data on water transport through the stratum corneum of the skin was initially reviewed and

compared with data relating to water transport through the nail. Although it was already known that antifungal drugs could be applied to a diseased nail and a local therapeutic effect may sometimes be induced, nobody had proposed the use of the nail itself and its reservoir properties for other than the local delivery of drugs to the nail e.g. for the treatment of local fungal disease. The concept of the present invention of systemic administration of drugs by this route is thus totally novel and unexpected. Furthermore, whereas the stratum corneum of the normal epidermis acts as an effective barrier preventing the transport of most substances through the skin into the system circulation, the finger and toe nails by way of contrast have a very much higher permeability for suitable drugs. Furthermore, whereas the stratum corneum is best able to absorb substances which exhibit an approximately 50:50 distribution between aqueous and lipid phases or are more lipophilic, finger and toe nails have been found to be able to absorb therapeutically active substances which are more hydrophilic.

It is, accordingly, a particular advantage of the invention that the range of therapeutically active substances which can be administered is not limited in the same way as the stratum corneum to particularly critical lipid/water solubility partition characteristics. Also, the compositions which are applied to the finger and toe nails do not need to be in the form of oil/water emulsions and effective compositions can be prepared which are essentially lipid-free. Furthermore, whereas it has been found that substances having molecular weights in excess of 1000 daltons usually fail to pass through the stratum corneum in satisfactory quantities, higher molecular weights substances could be administered in accordance with the invention via finger and toe nails.

Application of a therapeutically active substance in accordance with the invention has a further advantage that the active substances can be administered in a wide range of dosage amounts. Thus, for example, if a given composition is designed to provide a dosage amount of 10 milligrams of therapeutically active substance which is released over a 12 hour period, the dosage amount can be increased in multiples by applying the composition to 1, 2, 3... 20 finger and toe

nails. In other words, the dosage range may be varied by up to 20 times simply by selecting the number of nails to which the composition is applied. Also, because different nails have different surface areas (c.f. the thumb and first toe nails with the fifth finger and fifth toe nails) an even wider range of possible dosage rates can be achieved by applying the composition of the invention to different finger and toe nails. The rate of administration may be further adjusted by incorporating penetration enhancers.

Furthermore, by applying a therapeutically active substance to finger or toe nails in accordance with the invention, the therapeutically active substance can enter the systemic circulation without initially entering the hepatic circulation.

In formulating compositions for use according to the invention customary binding agents and film forming materials may be used. Thus, for example, any of the polymeric film forming substances normally used in nail varnishes may be used, provided that they are compatible with the therapeutically active substance. Examples include polyvinylacetate, acrylate and methacrylate esters and nitrocellulose.

Similarly, for other dosage forms such as those used in dermatological and cosmetic applications, the same range of adjuvants may be used for application to the nail for example emulsifying agents, surfactants, thickening agents, stabilisers, colorants, buffers, antioxidants, etc.

The concentration of therapeutically active substance can vary over a wide range but normally would not exceed about 100 or 200 milligrams per millilitre. Normally a concentration in the range of 10 micrograms to 100 milligrams per millilitre would be used, most preferably 0.1 to 50 milligrams per millilitre, and especially 0.5 to 20 milligrams per millilitre.

## PHARMACOLOGICAL TESTING

### 1. In Vitro Experiments

The transport of therapeutically active substances through nail tissue was examined for eleven drugs. The drugs included those used in conventional patch delivery systems and others which are not known to be delivered in this way. The drugs were chosen to include a range of molecular size, chemical characteristics - polar/non-polar, lipid/water solubility and a variety of pharmacological effects.

#### Method

A modified Franz cell was used, and normal big toe nails (mostly obtained after surgical removal for ingrowing nails or injury) were stuck between two sheets of Teflon with aligned holes, separating a donor from receptor reservoir. The nails were soaked in HEPES buffer pH7.4 for 24h, the donor reservoir was then served with 1ml volume of a solution of the drug in buffer (see Table 1 for dose concentrations) and the passage of the radio-isotope of the drug into the receptor reservoir was measured at timed intervals up to 36h. When the experiment was completed residual isotope was measured in the nail after incineration. Replicates were made for all the drugs studied.

The results are given in Table 1 and Figures 3 to 7.

Table 1 summarises evidence of transungular transport for all eleven drugs studied and Figures 3 to 7 are examples of plots and show that the rate of transungular transport was approximately linear stages of permeation. No attempt was made in these experiments to optimise the transport of the drugs and the maximal rates are likely to be appreciably greater than has been demonstrated.



TABLE 1

**Rates of penetration through human nail  
and size of drug reservoir contained in the nails**

Substance under Test	Nail Thickness	Administered Dose of Drug (mg) in 1ml HEPES	Rate ( $\mu\text{g}/\text{cm}^2/\text{h}$ )	Time for calc of rate (h)	Drug Content of Nail as % of Dose Administered
L-Nicotine* (free base)	1.43	510	97.8	12 - 36	1.08
$\beta$ -Oestradiol	1.53	0.003	$9.6 \times 10^{-5}$	8 - 36	2.61
Quinuclidinyl* benzilate	1.00	$1.95 \times 10^{-4}$	$7.0 \times 10^{-6}$	2 - 24	7.31
Verapamil HCl	0.75	30	3.3	12 - 36	16.3
Indomethacin	1.05	0.32	0.028	12 - 36	2.76
DL-Propranolol HCl	0.95	50	1.36	4 - 36	4.81
Melatonin	1.20	30	1.23	2 - 36	1.73
Morphine- $\beta$ -D-glucuronide	1.69	0.2	$15.0 \times 10^{-3}$	12 - 36	3.83
Acetylsalicylic acid	1.70	3.3	0.037	4 - 36	7.64
Clonidine HCl*	1.82	143	10.7	4 - 36	1.64
DAGO* (enkephalin analogue)	1.48	25	2.9	2-24	0.73

\*not a saturated solution

## 2. In Vivo Experiments

Different concentrations of nicotine were applied to different nails in a healthy individual, a non-smoker, not in contact with smokers, and nicotine and cotinine output were measured in 24h urine samples. The results are shown in Table 9. The samples were not light protected or refrigerated and are therefore indicative of lower levels of nicotine and cotinine than were originally present in the collected urine samples. Although they cannot be corrected for breakdown of nicotine and its metabolite after collection, nevertheless it can be seen that significant quantities of the nicotine and its metabolite were found in the urine. Furthermore on the day corresponding to the highest urinary output the subject, a non-smoker, experienced symptoms associated with nicotine administration.

The results appear in the following Table 2:

**TABLE 2**

	<u>sample</u>	<u>nicotine(<math>\mu</math>g/1)</u>	<u>cotinine(<math>\mu</math>g/1)</u>
1% Nicotine "peel off"	1	ND	ND
10% Nicotine "peel off"	2	ND	ND
10% in "water base"	3	ND	< 10
10% "water base" covered with 2% in nail lacquer	4	20	20
10% in water base	5	< 10	< 10

ND - non detected

The results from the *in vivo* study confirms the *in vitro* findings that transungual absorption of drugs occurs and can provide quantities of drugs sufficient for systemic therapeutic action. The *in vitro* studies used a range of drugs and absorption occurred with different levels of lipophilicity and water solubility, polarity, molecular size, etc. These results indicated that with suitably

adjusted vehicles, including enhancing agents if necessary, far more drug could be made to pass through the nail because of selective partitioning. Thus, we can predict that transungual absorption could be increased still further. Nevertheless the quantities which were absorbed through the nail were in many instances adequate to provide systemic therapeutic effects. Some, like nicotine and clonidine are well absorbed through the transdermal patch system and nail application would provide an alternative system, but others e.g. melatonin and the 5 amino acid peptide enkephalin which were absorbed in acceptable quantities, nail application provides distinct advantage over the transdermal system. From the degree of transport of an enkephalin molecule we believe that peptides, polypeptides and probably small proteins could be absorbed by the system. This would provide a great advantage for the administration of a number of peptide drugs and biological agents, including those capable of being produced by biotechnology techniques.

The results also demonstrate that the nail provides a significant large reservoir from which systemic absorption of drugs can proceed. Such a reservoir could supersede the use of an external reservoir as in a patch system, or indeed could be used further to amplify such a reservoir designed to compliment the specific characteristics of the nail. Thus, Table 1 shows the magnitude of the reservoir in the nails (demonstrated by combustion and radioisotopic measurement and expressed as a percentage of the drug material applied to the donor reservoir). In milligram terms, the figures were 5.49 for nicotine, 4.89 for verapamil HCl, 2.39 for DL-propranolol HCl, 2.35 for clonidine HCl and 0.14 for DAGO (enkephalin analogue, Tyr Ala Gly Phe Gly; obtainable under catalogue E7384 from Sigma Chemical Company).

The following examples illustrate the invention:

**Example 1**

A nicotine containing nail varnish was prepared by dissolving 2 wt% nicotine in a commercially available thixotropic nitrocellulose collodion sold by SNPE Chimie under the designation Suspension Base 320

**Example 2**

A second and third formulations were prepared as described in Example 1, but containing 5 wt% and 10 wt% nicotine.

**Example 3**

Formulations similar to those described in Examples 1 and 2 were prepared using a resin based thixotropic gel manufactured by SNPE Chimie and designated Thixotropic GEL 373.

**Example 4**

Formulations similar to those described in Examples 1-3 or alternatively in aqueous buffer solutions may be made using the drugs listed in Table 1.

**CLAIMS**

1. A method of administering a therapeutically active substance to a subject, which comprises applying the substance to the surface of one or more finger nails and/or toe nails whereby the substance is absorbed and transported systemically to a site of action remote from the finger or toe nail.
2. A method according to Claim 1 wherein the substance is applied in the form of a composition comprising one or more components for promoting retention of the composition on and/or in the nail surface.
3. A method according to Claim 1 or Claim 2 wherein the composition comprises one or more penetration enhancers.
4. A method according to any preceding claim wherein one or more components of the composition are contained in liposomes, niosomes or other vesicles.
5. A method according to any preceding claim wherein the composition is in the form of a varnish, lacquer, aerosol, gel, lotion, cream, ointment, subsaturated solution, saturated solution, supersaturated solution or patch.
6. A method according to any preceding claim wherein the therapeutically active substance has a therapeutic effect on the central nervous system, cardiovascular system or respiratory system.
7. A method according to any preceding claim wherein the therapeutically active substance has an analgesic, anti-allergic, anti-emetic or psychotropic effect.

## 20

8. A method according to any preceding claim wherein the therapeutically active substance has a therapeutic effect on the gastro-intestinal tract, genito-urinary system, or endocrine system.
9. A method according to any preceding claim wherein the therapeutically active substance has contraceptive activity, has activity as the active agent for hormone replacement therapy, or is capable of modulating the endocrine system or its effects on tissues.
10. A method according to any of Claims 1 to 5 wherein the active substance is antigenic whereby the composition acts as a vaccine.
11. A method according to any of Claims 1 to 5 wherein the therapeutically active substance acts as an immunomodulator.
12. A method according to any preceding claim wherein the therapeutically active substance is applied in an amount such that the nail or nails retain a reservoir of the substance for subsequent release.
13. The use of a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical composition adapted for application to finger nails and/or toe nails, characterised in that the composition contains at least one therapeutically active substance whereby in use the substance is absorbed and transported systemically to a site of action remote from the finger or toe nail.

## 21

14. The use of a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical composition adapted for application to finger nails and/or toe nails, characterised in that the composition contains at least one therapeutically active substance which is capable of passing from the applied composition, through the nail to which it is applied, and into a systemic tissue compartment.
15. The use as claimed in Claim 13 or Claim 14 wherein the pharmaceutical composition and/or therapeutically active substance is as defined in any of Claims 1 to 12.

1/4

Fig.1.

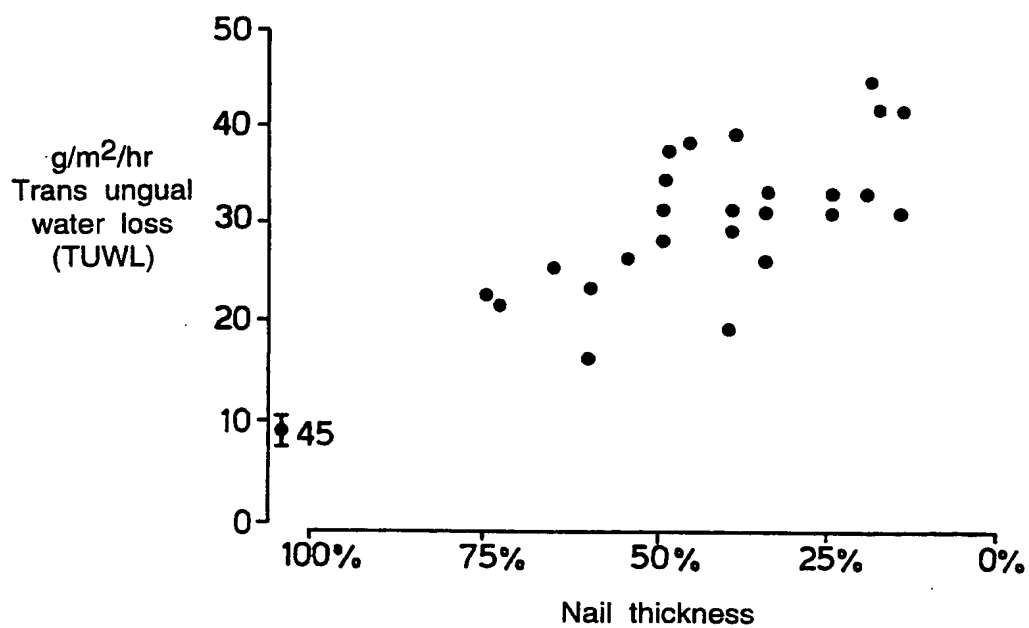
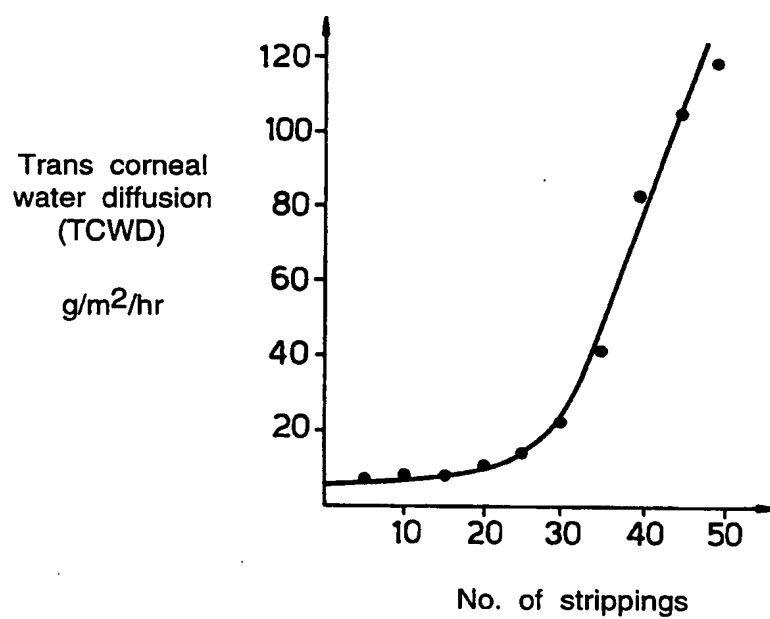


Fig.2.



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2/4

Fig.3.

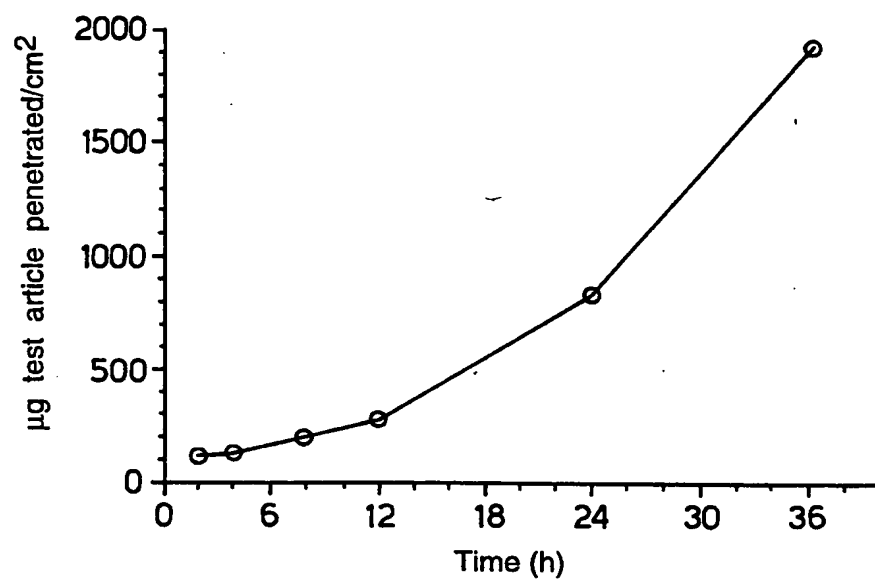
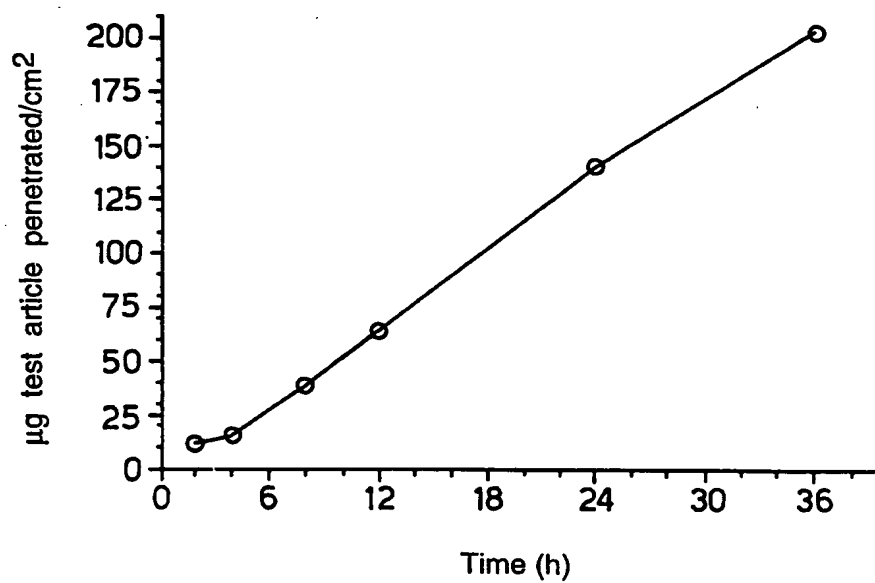


Fig.4.



3/4

Fig.5.

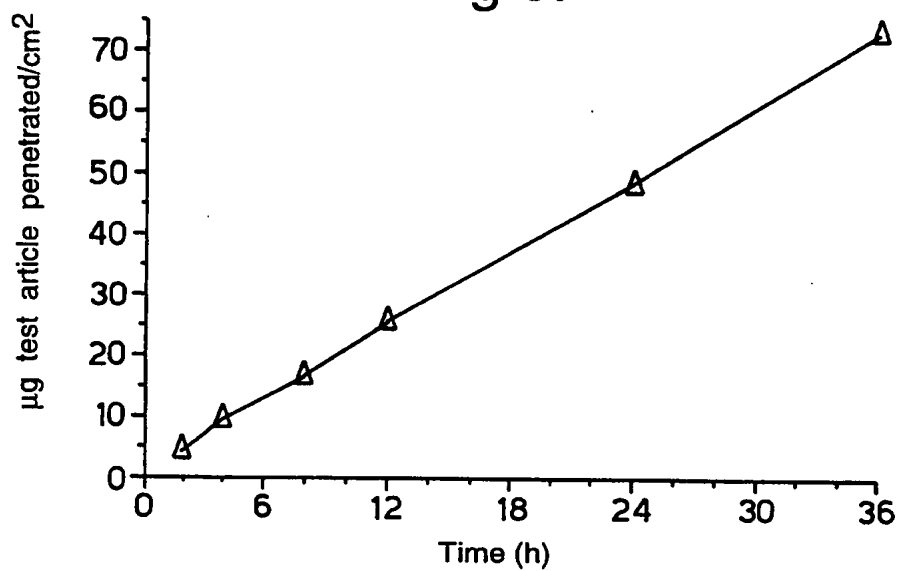
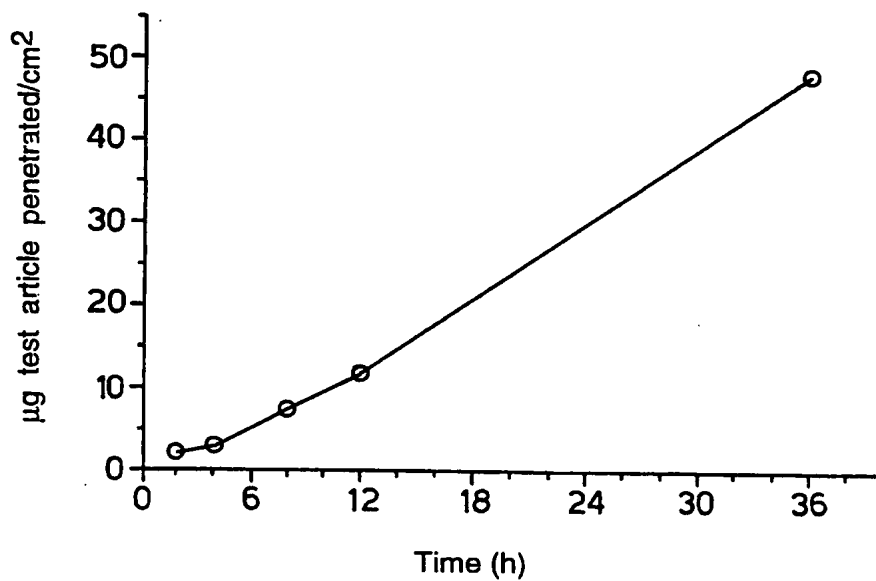
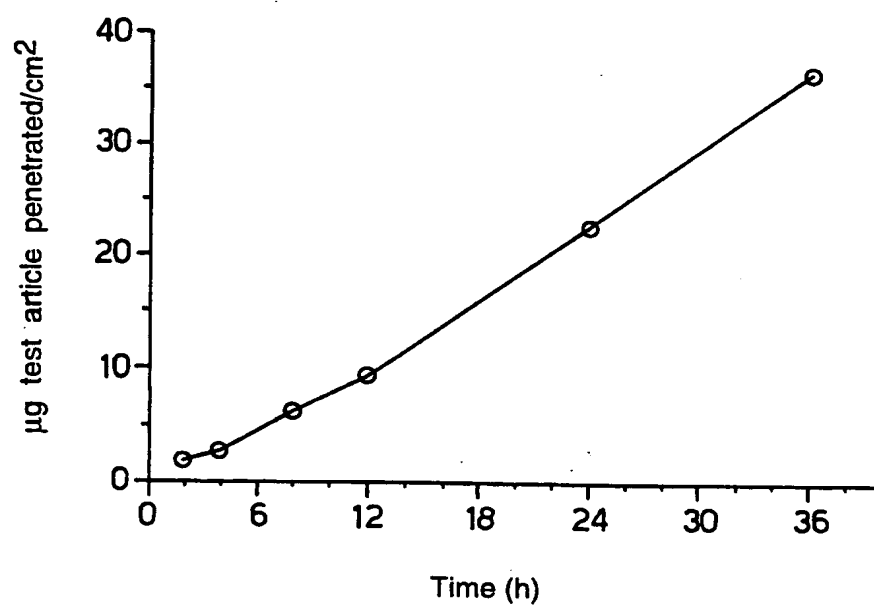


Fig.6.



4/4

Fig.7.



# INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No  
PCT/GB 95/00459

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K9/70 A61K7/043 A61K7/04 A61K31/465

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 206 493 (C.I.R.D.) 11 January 1989 cited in the application see page 1, line 4 - line 10 see page 7, line 6 - line 17 ---	13-15
X	INT. J. COSM. SCI., vol. 5, no. 6, December 1983 LOUGHBOROUGH, pages 231-246, WALTERS K.A. ET AL 'PERMEABILITY CHARACTERISTICS OF THE HUMAN NAIL PLATE' cited in the application see page 235, paragraph 6 - page 236, paragraph 1 see page 238; table 3 --- -/--	13-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

31 May 1995

Date of mailing of the international search report

18.06.95

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## INTERNATIONAL SEARCH REPORT

Inter. natl Application No

PCT/GB 95/00459

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SKIN PHARM., vol. 5, no. 3, September 1992 WOOLBRIDGE, pages 154-159, MAYER P. ET AL 'TOPICAL AND SYSTEMIC ABSORPTION OF SODIUM PYRITHIONE FOLLOWING TOPICAL APPLICATION TO THE NAILS OF THE RHESUS MONKEY' cited in the application see page 154 ---	13-15
A	J. PHARM. PHARMACOL., vol. 35, no. 1, January 1983 pages 28-33, WALTERS K.A. ET AL 'PHYSICOCHEMICAL CHARACTERIZATION OF THE HUMAN NAIL : PERMEATION PATTERN FOR WATER AND THE HOMOLOGOUS ALCOHOLS AND DIFFERENCES WITH RESPECT TO THE STRATUM CORNEUM' cited in the application see the whole document ---	13-15
A	CA,A,1 273 878 (MOODY R.) 11 September 1990 cited in the application see page 14; example 7 ---	13-15
A	WO,A,87 02580 (DERMATOLOGICAL PRODUCTS OF TEXAS) 7 May 1987 cited in the application see page 5, line 14 - line 17 see page 15; example 4 -----	13-15

# INTERNATIONAL SEARCH REPORT

1. International application No.

PCT/GB95/00459

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **claims 1-12**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Method of treatment of the human body by therapy Rule 39.1(IV)**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Application No

PCT/GB 95/00459

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-2206493	11-01-89	FR-A- 2616333 CA-A- 1315853 CH-A- 676427	16-12-88 06-04-93 31-01-91
CA-A-1273878	11-09-90	NONE	
WO-A-8702580	07-05-87	AU-B- 599064 AU-A- 6627886 DE-A- 3687458 EP-A,B 0247142 JP-T- 1501143	12-07-90 19-05-87 18-02-93 02-12-87 20-04-89